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Natural products in attenuating renal inflammation *via* inhibiting the NLRP3 inflammasome in diabetic kidney disease

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Diabetic kidney disease (DKD) is a prevalent and severe complications of diabetes and serves as the primary cause of end-stage kidney disease (ESKD) globally. Increasing evidence indicates that renal inflammation is critical in the pathogenesis of DKD. The nucleotide - binding oligomerization domain (NOD) - like receptor family pyrin domain containing 3 (NLRP3) inflammasome is the most extensively researched inflammasome complex and is considered a crucial regulator in the pathogenesis of DKD. The activation of NLRP3 inflammasome is regulated by various signaling pathways, including NF- κB, thioredoxin—interacting protein (TXNIP), and non-coding RNAs (ncRNA), among others. Natural products are chemicals extracted from living organisms in nature, and they typically possess pharmacological and biological activities. They are invaluable sources for drug design and development. Research has demonstrated that many natural products can alleviate DKD by targeting the NLRP3 inflammasome. In this review, we highlight the role of the NLRP3 inflammasome in DKD, and the pathways by which natural products fight against DKD *via* inhibiting the NLRP3 inflammasome activation, so as to provide novel insights for the treatment of DKD.

KEYWORDS

natural products (NP), diabetic kidney disease (DKD), inflammation, the NLRP3 inflammasome, NF- κB, TXNIP (thioredoxin interacting protein)

1 Introduction

Diabetic kidney disease (DKD) is one of the most prevalent and severe microvascular complications of diabetes, and is also the main cause of end stage kidney disease (ESKD) globally. Approximately 30% to 50% of ESKD cases worldwide are attributed to DKD (1). The pathogenesis of DKD is multifaceted, involving metabolic abnormalities, renal hemodynamics changes, oxidative stress, and inflammation, among others.

Initially, metabolic and hemodynamic changes were believed to be the main factors in the development of DKD. However, it is gradually realized that inflammation plays an important role in the development and progression of DKD (2, 3). Chronic exposure to advanced glycation end products (AGEs) stimulates the release of chemokines and cytokines, which can be recognized by Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs), leading to heightened inflammatory responses. Persistent inflammation ultimately results in the onset of DKD (4).

Natural products include a diverse group of substances extracted from various natural sources such as plants, bacteria, fungi, insects, and even animals, they are valuable sources for drug design and development (5). Accumulative evidence demonstrates that many natural products could suppress systemic and renal inflammation by targeting nuclear transcription factor-κB (NF-κB), NLR family pyrin domain containing 3 (NLRP3) inflammasome, transforming growth factor-β (TGF-β) signaling pathway, and exhibit reno-protective effects on DKD (6). The NLRP3 inflammasome is a critical regulator of inflammation in DKD and is considered a potential therapeutic target (7). In this review, we highlight the role of NLRP3 inflammasome in DKD, and the pathways by which natural products fight against DKD *via* inhibiting the NLRP3 inflammasome activation, so as to offer novel insights for the treatment of DKD.

2 A brief overview of the NLRP3 inflammasome in DKD

As a member of NLR, NLRP3 can assemble into the NLRP3 inflammasome after recognizing danger signals, and exert biological effects by activating caspase-1 and promoting the maturation and secretion of interleukin (IL)-1β and IL-18. The NLRP3 inflammasome is a multiprotein complex composed of NLRP3, apoptosis-associated speck-like protein (ASC), and caspase-1. Among them, NLRP3 is the core protein, containing three different domains. First is the pyrin domain (PYD) or C-terminal caspase-recruitment domain (CARD), located on the N-terminus. It can bind to other proteins, and mediate signal transduction. Second is the NACHT domain located in the middle, responsible for activating the NLRP3 inflammasome through ATP-dependent oligomerization. Third is the leucine-rich repeat (LRR) domain, which located on the C-terminus, and is responsible for identifying pathogenic organisms and endogenous danger signals. ASC is an adaptor protein that connects upstream NLRP3 to downstream caspase-1. Caspase-1 is the effector protein in NLRP3 inflammasome, it induces the production and IL-1β and IL-18, resulting in inflammation (8).

3 The NLRP3 inflammasome regulator in DKD

NLRP3 is widely expressed in glomerular and tubular epithelial cells of DKD patients and mice. Inhibition of NLRP3, ASC, or caspase-1 can reduce the damage of podocytes, endothelial cells and mesangial cells, and can also significantly reduce the inflammatory response of tubulointerstitium. NLRP3 knockout improved renal pathological changes in diabetic mice (4, 9, 10). These findings suggest that the NLRP3 inflammasome plays a significant role in DKD.

The activation of the NLRP3 inflammasome is a two-step process. The "priming step" is the first phase, involving recognition of danger signals by TLR and activation of NF-κB, which will up-regulate the expression of NLRP3, pro-IL-1β and pro-IL-18. The "activating step" is the second phase, triggered by potassium efflux, calcium influx, mitochondrial dysfunction, lysosomal disruption and reactive oxygen species (ROS) overproduction. These danger signals promote the formation of the NLRP3 inflammasome (11–13). It is found that multiple signaling pathways can exacerbate DKD by targeting the NLRP3 inflammasome activation (Table 1).

TABLE 1 Signaling pathways regulating the NLRP3 inflammasome activation in DKD.

Signaling Pathways	*In vivo/in vitro*	Model	Findings	References
NF-κB	*In vitro*	Mouse podocytes	TLR4 knockdown inhibited NLRP3 inflammasome	(14)
	In vivo, in vitro	Db/db mice mouse mesangial cell	TLR9 knockdown inhibited NF-κB and NLRP3 inflammasome	(15)
	In vivo, in vitro	DKD Patients HFD/STZ mice MPC5	FOXM1 activated SIRT4, inhibited NF-κB and NLRP3 inflammasome	(16)
	In vivo, in vitro	Db/db mice STZmice DKD Patients HK-2 cells	CXCL1/CXCR2 activated NF-κB and the NLRP3 inflammasome	(17)
TXNIP	*In vivo, in vitro*	STZ rats HK-2 cells	TXNIP promoted NLRP3 inflammasome activation	(18)

(Continued)

TABLE 1 Continued

Signaling Pathways	*In vivo/in vitro*	Model	Findings	References
	In vivo, in vitro	DKD Patients STZ mice human podocyte cell line	TXNIP activated NADPH oxidase and then triggered NLRP3 inflammasome activation	(19)
	In vivo, in vitro	STZ rats Rat glomerular mesangial cells	ROS inhibitor down-regulated TXNIP, NLRP3 and IL-1β	(20)
	In vivo, in vitro	db/db mice HK-2 cells	mtROS upregulated TXNIP, NLRP3 and IL-1β	(21)
	In vivo	HFD/STZ Rats	IRE1stimulated TXINP and NLRP3	(22)
	In vivo, in vitro	STZ mice Human podocyte cell line	EZH2/EGR1/TXNIP/NLRP3 pathway contributed to DKD	(23)
	In vivo, in vitro	Db/db mice NRK52E cell line	Sphingosine kinase 2 activated TXINP, NLRP3, and IL-1β	(24)
	In vitro	Human glomerular podocytes	NOX4 upregulated NLRP3	(25)
	In vivo, in vitro	STZ rats Mouse podocytes	Icariin inhibited NLRP3 by Keap1-Nrf2/HO-1 pathway	(26)
	In vivo	Db/db mice	Minocycline stabilized Nrf2 and inhibited NLRP3	(27)
	In vivo	STZ mice	Berberine stabilized Nrf2 and inhibited NLRP3	(28)
	In vivo	STZ rats	Zinc Oxide Regulated Nrf2/TXNIP/NLRP3 Inflammasome pathway	(29)
	In vivo, in vitro	db/db mice HK-2 cells	CD36 promoted mtROS and NLRP3	(30)
	In vivo, in vitro	STZ mice Mouse proximal tubular cells	Activated Protein C inhibited ROS and NLRP3	(31)
	In vitro	Mouse glomerular mesangial cells	RIPK2 inhibited ROS and NLRP3 inflammasome	(32)
	In vivo, in vitro	DKD patients Murine renal tubular epithelial cells	Optineurin reduced mtROS and inhibited NLRP3 inflammasome	(33)
Non-coding RNAs	*In vivo, in vitro*	DKD patients STZ mice& db/db mice Human podocytes	MiRNA-10 negatively regulated NLRP3	(34)
	In vitro	Mouse glomerular podocyte line	MiRNA-29a inhibited NLRP3	(35)
	In vivo, in vitro	DKD Patients HK-2 cells	MiR-520c-3p inhibited TXNIP/NLRP3	(36)
	In vivo, in vitro	STZ rats HK-2 cells	lncRNA-MALAT1 down-regulated miR-23c and up-regulated NLRP3	(37)
	In vitro	MPC-5 cells	Atorvastatin protected podocytes by regulating MALAT1/miR-200c/Nrf2	(38)
	Vitro	HK-2 cells	lncRNA-MALAT1 down-regulated miR-30c and up-regulated NLRP3	(39)
	In vivo, in vitro	STZ rats HBZY-1 cells	lncRNA-NEAT1 down-regulated miR-34c and up-regulated NLRP3	(40)
	In vitro	HK-2 cells	lncRNA-NEAT2 down-regulated miR-206 and up-regulated NLRP3	(41)
	In vivo, in vitro	STZ rats HK-2 cells	lncRNA-XIST down-regulated miRNA-15b-5p, upregulated TLR4 and NLRP3	(42)
	In vivo, in vitro	DKD patients HK-2 cells	lncRNA-KCNQ1OT1 down-regulated miRNA-506-3p and up-regulated NLRP3	(43)
	In vitro	HK-2 cells	lncRNA-GAS5 down-regulated miR-452-5p and NLRP3	(44)
	In vitro	Mouse podocyte cell line	sC5b-9 promoted NLRP3 activation *via* up-regulating Kcnq1to1and down-regulating mRNA-486a-3p	(45)

(Continued)

TABLE 1 Continued

Signaling Pathways	*In vivo/in vitro*	Model	Findings	References
	In vivo, in vitro	DKD patients HK-2 cells	lncRNA-ANRIL down-regulated miRNA-497, and up-regulated TXNIP/NLRP3	(46)
	In vitro	Mouse mesangial cells	lncRNA-Gm4419 knockdown inhibited NF-κB and NLRP3	(47)
	In vivo, in vitro	DKD patients HK-2 cells	Circ_0004951 down-regulated miRNA-93-5p, and up-regulated NLRP3	(48)
Interleukin	*In vivo*	Db/db mice	Blockade of IL-6 receptor inhibited NLRP3 by regulating IL-17A	(49)
	In vivo, in vitro	DKD patients STZ mice HEK293T cells	IL-22 inhibited NLRP3/caspase-1/IL-1β	(50)
	In vitro	Mouse Podocyte	IL-37 inhibited NLRP3	(51)
BTK	*In vivo*	DKD patients STZ mice	BTK activated NLRP3 inflammasome	(52)
	In vivo, in vitro	HFD mice Murine bone marrow-derived macrophages Human monocyte-derived macrophages	BTK inhibitor suppressed NLRP3 *via* regulating IRS-1/Akt/GSK-3β	(53)
GSK-3β/HIF-1α	*In vitro*	Mouse renal proximal tubular epithelial cells	GSK-3β knockdown decreased NLRP3	(54)
HDAC6	*In vivo, in vitro*	DKD patients STZ mice Mouse Bone Marrow–Derived Macrophages HK-2 cells	HDAC6 inhibitor suppressed NLRP3 inflammasome	(55)
RIPK3	*In vivo*	STZ mice	RIPK3 controls cellular signaling through the formation of NLRP3	(56)
Syk/JNK	*In vivo, in vitro*	STZ rats HK-2 cells Rat glomerular mesangial cells	Syk/JNK activated NLRP3	(57)
PPARs	*In vivo*	Sugar-induced mice with diabesity	PPAR-δ agonists inhibited NLRP3	(58)
RAC1	*In vivo, in vitro*	Db/db mice HEK293T cells	RAC1 binding to NLRP3 activates the NLRP3 inflammasome	(59)
Spop	*In vivo, in vitro*	STZ mice Mice podocytes	Spop promoted NLRP3 degradation	(60)
WTAP	*In vivo, in vitro*	DKD patients HK-2 cells	WTAP upregulated NLRP3	(61)

CXCL1, Chemokine (C-X-C motif) Ligand 1 Protein; CXCR2, CXC chemokine receptor 2; EGR1, Early Growth Response Protein 1; EZH2, Enhancer of zeste homolog 2; FOXM1, Forkhead box M1; GSK-3β, Glycogen synthase kinase-3β; HDAC6, Histone deacetylase 6; HFD, High-Fat Diet; HIF, Hypoxia inducible factor; IRE1, Inositol-requiring enzyme 1; JNK, c-Jun N-terminal kinase; MPC, mouse podocyte cell; NLRP3, The nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3; NOX4, Nicotinamide Adenine Dinucleotide Phosphate Oxidase 4; PPARs, Peroxisome-proliferator activated receptors; RAC1,Ras-related C3 botulinum toxin substrate 1; RIPK, Receptor interacting protein kinase; ROS, reactive oxygen species; SIRT4, sirtuin 4; STZ, Streptozocin; Spop, Speckle-type POZ protein; Syk, Spleen tyrosine kinase; TLR, Toll-like receptors; TXNIP, thioredoxin-interacting protein; WTAP, Wilms tumor 1-associated protein.

3.1 NF-κB/NLRP3 signaling pathway

NF-κB is a transcription factor in the form of p50/p65 heterodimer. Normally, NF-κB binds to its inhibitor kappa B (IκB) and becomes inactive. When stimulus signals activate IκB kinase, IκB-α is phosphorylated and degraded, allowing NF-κB and IκB are dissociated and translocated into nucleus, where they regulate the expression of target genes (62). Liu et al. (14) revealed that high glucose (HG) promoted the activation of NLRP3 inflammasome in mouse podocytes (MPCs). The expression of TLR4 was also upregulated, which is an important signaling molecule regulating NF-κB. TLR4 knockdown inhibited the activation of NLRP3 inflammasome, attenuated HG-induced cell apoptosis, and increased cell viability. Shen et al (15) found that TLR9 knockdown would inhibit NF-κB/NLRP3 pathway in HG-induced Mesangial Cells (MCs). Furthermore, inhibition of TLR9 reduced NF-κB and NLRP3 expression, and decreased microalbuminuria, renal inflammatory response, and glomerular

lesion in db/db mice. Xu et al (16) demonstrated that Forkhead box M1(FOXM1) transcriptionally activated sirtuin 4 (SIRT4) and inhibited NF-κB signaling and the NLRP3 inflammasome, thereby alleviating renal injury *in vivo* and *in vitro*. Tang et al. (17) also confirmed that CXCL1/CXCR2 may cause inflammation in HK-2 cells with HG treatment by phosphorylating NF-κB and activating the NLRP3 inflammasome. Li et al. (63) found that the activation of AMPK/SIRT1 pathway promoted the expression of NF-κB, NLRP3, ASC, Caspase-1, and IL-1β in DKD mice.

3.2 TXNIP/NLRP3 signaling pathway

Thioredoxin-interacting protein (TXNIP) is an alpha-arrestin protein with a molecular weight of 46 kD. It can bind to thioredoxin (TRX) and interfere with its expression, which is an essential regulator of oxidative stress, cell proliferation, and apoptosis (64, 65). It has been revealed that TXNIP is released from oxidized TRX under oxidative stress, resulting in the activation of NLRP3 inflammasome (66).

There is abundant evidence that TXNIP/NLRP3 signaling pathway is involved in the inflammatory response of DKD. For instance, Gu et al. (18) revealed that TXNIP and NLRP3 were overexpressed in the renal tissue of DKD rats. It is also observed that HG stimulated TXNIP/NLRP3, promoting inflammation. Gao et al. (19) found that HG-promoted Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase activation *via* TXNIP, which in turn activated the NLRP3 inflammasome, leading to podocyte injury. It has also been revealed that HG activates ROS/TXNIP/NLRP3 inflammasome signaling in glomerular mesangial cells (20), and mitochondrial ROS(mt ROS)/TXNIP/NLRP3 pathway is involved in tubular oxidative injury in DKD (21). Furthermore, it has been confirmed that many molecules participate in the pathogenesis of DKD by regulating TXNIP/NLRP3 inflammasome pathway. Inositol-requiring enzyme 1α (IRE1α), an endoplasmic reticulum transmembrane sensor, can stimulate TXINP/NLRP3 signaling pathway and aggravate DKD in rat model (22). Enhancer of zeste homolog 2 (EZH2), a subunit of the polycomb repressive complex 2, contributes to S-adenosylhomocysteine inhibition-aggravated DKD in mice through EZH2/EGR1/TXNIP/NLRP3 signaling pathway (23). Sphingosine kinase 2 (SphK2) is a key enzyme catalyzing the formation of sphingosine-1-phosphate. Research shows that SphK2 increases TXNIP, NLRP3 inflammasome and IL-1β levels, induces inflammation, promotes renal tubular epithelial cell damage, leading to DKD aggravation (24).

Additionally, there is substantial evidence that many molecules contribute to DKD progression through the ROS/NLRP3 inflammasome pathway. It is found that NADPH oxidase 4 (NOX4), a major source of ROS, is upregulated in HG-induced podocytes. Suppression of NOX4 inhibits the activation of NLRP3 inflammasome and alleviates podocytes apoptosis (25). Nuclear factor E2-related factor 2 (Nrf2) is a transcription factor that protects cells from oxidative stress (67) and serves as most sensitive signal of scavenging ROS under oxidative stress (68). It is reported that Nrf2 may alleviate DKD by suppressing the activation of NLRP3 inflammasome (26–29). CD36, a fatty acid transporter, causes renal tubular epithelial cell injury by activating mtROS/NLRP3 pathway in DKD (30). Activated protein C (aPC), an endothelial-dependent cytoprotective coagulation protease, meliorates tubular mitochondrial ROS and inflammation in DKD (31). Receptor interacting protein kinase 2 (RIPK2) has also been confirmed to negatively regulate ROS/NLRP3 signaling in mouse glomerular mesangial cells treated with HG (32). Optineurin, a well-recognized autophagy receptor, reduces the activation of NLRP3 inflammasome by reducing mtROS and mitophagy in HG -treated renal tubular cells (33).

3.3 Non-coding RNAs

Non-coding RNAs (ncRNAs) are recognized as a class of ribonucleic acids (RNAs) that are not translated into proteins. ncRNAs consist of various family members, including microRNAs (miRNAs), long ncRNAs (lncRNAs), ribosomal RNAs, transfer RNAs, circular RNAs(circ-RNAs), and others. Different classes of ncRNAs engage in different cellular processes, regulating gene expression, RNA maturation, and protein synthesis (69).

MiRNAs are small ncRNAs that regulate gene expression through recognizing cognate sequences and interfering with transcriptional, translational, and epigenetic processes. Many miRNAs have been shown to participate in the pathogenesis of DKD by regulating the NLRP3 inflammasome. For example, Ding et al (34) found that miRNA-10 alleviated inflammation in DKD by reducing the NLRP3 inflammasome activation. Zhang (35) demonstrated that miRNA-29a inhibited HG-induced podocytes pyroptosis and alleviated inflammatory response by directly targeting NLRP3. Song et al (36) revealed that miR−520c−3p reduced HK-2 cell pyroptosis induced by HG through inhibiting TXNIP/NLRP3 inflammasome pathway.

LncRNAs are defined as ncRNAs containing more than 200 nucleotides in length (70). They act through numerous paradigms and are key regulatory molecules in cells (71). It is found that in diabetic rats and HG treated podocytes/renal tubule (HK-2) cells, the up-regulation of lncRNA-MALAT1 promoted the NLRP3 inflammasome activation *via* inhibiting miR-23c (37), miR-200c (38) and miR-30c (39). In addition, many other lncRNAs have also been confirmed to take part in the development of DKD by targeting NLRP3 inflammasome, such as lncRNA-NEAT1/miR-34c (40), lncRNA NEAT2/miR-206 (41), lncRNA-XIST/miR-15b-5p (42), lncRNA-KCNQ1OT1/miR-506-3p (43), lncRNA-GAS5/miR-452-5p (44), Kcnq1ot1/miR-486a-3p (45), lncRNA-ANRIL/miR-497 (46), and lncRNA-Gm4419 (47).

Circular RNAs(circ-RNAs) are a class of ncRNAs that lack the 5' or 3' end. They regulate gene expression by pervading the transcription, the mRNA turnover, and translation. It is showed that Circ_0004951 is significantly up-regulated in DKD, where it can suppress miR-93-5p and activate NLRP3 inflammasome (48).

3.4 Others

Interleukin (IL): ILs are a type of cytokine released by various cells, playing a crucial role in immune regulation and homeostasis. Many ILs have been confirmed to be involved in renal damage caused by diabetes through the regulation of the NLRP3 inflammasome. Wu et al. (49) found that blocking the IL-6 receptor inhibited the NLRP3 inflammasome by restraining IL-17A. Wang et al. (50) demonstrated that IL-22 has reno-protective effects on DKD by downregulating renal NLRP3/caspase-1/IL-1β pathway. Zhang et al. (51) found that IL-37 decreased the expression of NLRP3, ASC, and caspase-1 in HG-treated podocytes.

Bruton's tyrosine kinase (BTK): BTK, an intracellular non-receptor tyrosine kinase, is considered as an vital signal in immunoregulation (72). It has been observed that BTK activates the NLRP3 inflammasome and promotes renal inflammation in diabetic patients and mice (52). BTK inhibitor attenuates NLRP3 inflammasome activation and alleviates DKD (53).

Glycogen synthase kinase (GSK)-3β/Hypoxia inducible factor (HIF)-α: GSK-3β, a serine/threonine kinase, is crucial for glycogen synthesis by regulating phosphorylation of glycogen synthase (73). It is found that HIF-1α is also a direct target of GSK-3β (74). Inhibition of the GSK-3β/HIF-1α pathway has been shown to alleviate NLRP3-induced pyroptosis in HG-treated renal tubular epithelial cells (54).

Histone deacetylase 6 (HDAC6):HDAC6 is a cytoplasmic enzyme that participates in a variety of cellular processes (75). Inhibition of HDAC6 has been shown to ameliorate DKD by suppressing the NLRP3 inflammasome (55).

Receptor-interacting protein kinase-3 (RIPK3): RIPK3 is a multifunctional regulator of cell death and inflammation. It is reported that RIPK3 is associated with renal fibrosis in DKD by activating NLRP3 inflammasome. Blockade of RIPK3 attenuates tubulointerstitial fibrosis (56).

Spleen tyrosine kinase (Syk)/c-Jun N-terminal kinase (JNK)/NLRP3 signaling pathway: Syk is a non-receptor protein tyrosine kinase. Inhibition of Syk has been shown to downregulate JNK expression and suppress the activation of the NLRP3 inflammasome stimulated by HG, indicating that the Syk/JNK/NLRP3 pathway may play a role in the inflammatory injury in DKD (57).

Peroxisome-proliferator activated receptors (PPARs): PPARs belong to the nuclear receptor superfamily, with three subtypes: PPAR-α, PPAR-γ, and PPARβ/δ. They regulate glucose and lipid metabolism and also mediate inflammation (76). It is reported that PPAR-δ agonist attenuates renal dysfunction and inflammation by preventing activation of the NLRP3 inflammasome in diabesity mice (58).

Ras-related C3 botulinum toxin substrate 1 (RAC1): RAC1 is a member of the Rho family of small GTPases and plays a role in cell proliferation, apoptosis, and inflammation (77, 78). It is revealed that RAC1 binding to NLRP3 activates the NLRP3 inflammasome in the kidney and accelerates DKD pathological processes (59).

Speckle-type POZ protein (Spop): Spop, an E3 ubiquitin ligase, is involved in many cellular processes by promoting the degradation of its target proteins (79, 80). It is observed that Spop inhibits the NLRP3 inflammasome and ameliorates DKD, the possible mechanism is that Spop may directly contact with NLRP3 and promote NLRP3 degradation *via* elevating K48-linked polyubiquitination of NLRP3 (60).

Wilms tumor 1-associated protein (WTAP): WTAP is a critical constituent of the classical m6A methyltransferase, which may cause modification of NLRP3. It has been demonstrated that WTAP upregulates the expression of NLRP3 by increasing the m6A methylation of NLRP3 mRNA, leading to inflammatory response (61).

4 Natural products alleviating DKD *via* targeting the NLRP3 inflammasome

Natural products are chemicals extracted from living organisms, and usually have pharmacological or biological activities. They are highly beneficial for drug design and development. Numerous natural products have been found to alleviate DKD by targeting the NLRP3 inflammasome (Table 2 and Figures 1, 2).

4.1 Flavonoids

Flavonoids refer to a series of compounds formed by two benzene rings connected to each other by three carbon atoms, that is, with a C_6-C_3-C_6 structure (129). Natural flavonoids are classified based on their basic structure into flavones, flavanones, isoflavones, flavonols, anthocyanins, and flavan-3-ols. They are widely found in plants.

Naringin is a bioflavonoid mainly found in the fruits of Citrus paradisi Macfadyen, grapefruit, tangerine, and oranges. It appears to have antioxidant, anticancer, and anti-atherosclerosis properties. It is reported that naringin could lower glucose levels (130–132). In rat glomerular mesangial cells induced by HG, the expressions of NLRP3 were significantly higher. Pre-treatment with naringin alleviated the activation of NLRP3 inflammasome, and inhibited cell proliferation (81).

Quercetin (Qu) is a plant flavonoid widely exist in apples, grapes, tomatoes, and onions, etc. Its structure contains phenolic hydroxyl groups and double bonds, which provide strong antioxidant activity (133). Dihydroquercetin (DHQ), also known as taxifolin, is the reduced form of Qu. It is a major dihydroflavone compound derived from Larix sibirica Ledeb. and Pseudotsuga taxifolia (Lamb.) Britton (134). These two natural compounds exert numerous biological activities, including antioxidant, anti-inflammation, antitumor, antiviral effects (135–139). Wang et al. (82) found that Qu can suppress the NLRP3 inflammasome activation in kidney, ameliorating kidney lipid accumulation in STZ-treated rats. A meta-analysis of rodent data (140) also showed that Qu significantly improved renal function, urinary protein excretion, and renal pathological changes in DKD. Regarding the underlying mechanisms, Qu may provide renoprotection in DKD

TABLE 2 Natural products in alleviating DKD by targeting the NLRP3 inflammasome.

	Compounds	Resource	*In Vivo/ in Vitro*	Model	Signaling Pathways	References
Flavonoids	Naringin	Grapefruit and citrus fruit	*In vitro*	Glomerular mesangial cells	InhibitedNLRP3	(81)
	Quercetin	Apples, grapes, tomatoes, and onions	*In vivo*	STZ rats	InhibitedNLRP3	(82)
	Dihydroquercetin	Larix sibirica Ledeb. and Pseudotsuga taxifolia (Lamb.) Britton	*In vivo, in vitro*	HFD/STZ rats HBZY-1 and HK2 cell cells	InhibitedROS and NLRP3	(83)
	Fisetin	Vegetables and fruits, apples, persimmons, grapes, strawberries, cucumbers, and onions.	*In vivo, in vitro*	STZ mice Mouse podocytes	Inhibited NLRP3 inflammasome	(84)
	Fisetin	As above	*In vivo, in vitro*	HFD mice HK-2 cells	InhibitedRIP3/NLRP3	(85)
	Liquiritigenin	Glycyrrhizae radix	*In vitro*	HBZY-1	Decreased NOX4, NF-κB and NLRP3	(86)
	Isoliquiritigenin	As above	*In vivo*	STZ rats	Up-regulated Sirt-1 and inhibited NF-κB/NLRP3	(87)
	Icariin	Herba epimedii	*In vivo, in vitro*	STZ rats MPC-5	Inhibited NLRP3 *via* Keap1-Nrf2/HO-1 axis	(26)
	Calycosin	Radix Astragali	*In vivo*	STZ rats	InhibitedNF-κB/p65/NLRP3/ TXNIP	(88)
	Luteolin	Fruits and vegetables	*In vitro*	MPC-5	InhibitedNLRP3	(89)
	Complanatoside A	Semen Astragali Complanati	*In vivo, in vitro*	STZ mice HK-2 cells	InhibitedNOX4 and NLRP3	(90)
	Kaempferol	Sand ginger	*In vivo*	STZ rats	InhibitedNLRP3	(91)
	Carithamine	Safflower	*In vivo*	STZ rats	Down-regulated NLRP3	(92)
Saponins	Ginsenoside Rg1	Ginseng	*In vivo, in vitro*	STZ rats Mouse podocyte cell line BNCC337685	Inhibited mTOR/NF-κB/NLRP3	(93)
	Ginsenoside Rg5	Black ginseng	*In vivo*	STZ mice	InhibitedROS, Nox4, TXNIP, NF-κB, MAPK, and NLRP3	(94)
	Ginsenoside compound K	Diol-type ginsenosides	*In vivo, in vitro*	STZ mice HBZY-1	InhibitedROS/NLRP3 and NF-κB/p38	(95)
	Sarsasapogenin	Anemarrhena asphodeloides Bunge	*In vivo, in vitro*	STZ rats Human mesangial cells	Suppressed NLRP3 and NF-κB by down-regulating PAR-1	(96)
	Sarsasapogenin	As above	*In vivo*	STZ rats	InhibitedNLRP3	(97)
	Astragaloside IV	Astragalus membranaceus	*In vivo, in vitro*	Db/db mice Mouse podocytes	InhibitedNLRP3	(98)
	Astragaloside IV	As above	*In vitro*	Mouse mesangial cells (SV40)	Inhibited ROS and NLRP3	(99)

(Continued)

TABLE 2 Continued

	Compounds	Resource	*In Vivo/ in Vitro*	Model	Signaling Pathways	References
	Salidroside	Rhodiola rosea	*In vitro*	HBZY-1	InhibitedTXNIP-NLRP3	(100)
	Notoginsenoside Fc	Panax notoginseng	*In vivo*	Db/db mice	Inhibited NLRP3	(101)
Phenolics	Tetrahydroxy stilbene glucoside	Polygoni Multiflori Radix	*In vitro*	MPC5	Inhibited NLRP3	(102)
	Gastrodin	Gastrodia elata	*In vitro*	MPC-5 cells	Actived AMPK/Nrf2 and inhibited NLRP3	(103)
	Epigallocatechin-3-gallate	Green tea	*In vivo*	HFD/STZ rats	suppressed endoplasmic reticulum stress-mediated NLRP3 inflammasome overactivation	(104)
	Resveratrol	Grape skin and red wine	*In vivo, in vitro*	STZ rats HK-2 cells	Inhibited TXNIP binding to NLRP3	(105)
	Piceatannol	Grapes, sugar cane, white tea, rhubarb, passion fruit and blueberries	*In vitro*	Mouse podocytes	Upregulated Nrf2 and NLRP3	(106)
	Curcumin	Rhizome Curcuma longa- turmeric	*In vivo, in vitro*	Db/db mice HK-2 cells	InhibitedNLRP3	(107)
	Punicalagin	Pomegranate, myrobalan, leaves of yellow wood, and tropical almond	*In vivo*	HFD/STZ mice	Downregulated NOX4, TXNIP, and NLRP3	(108)
	Purple Sweet Potato Color	Ipomoea batatas	*In vivo*	HFD mice	Suppressed VEGFR2/ROS/ NLRP3	(109)
	Grape seed proanthocyanidin	Grape seeds	*In vivo*	STZ rats	InhibitedNLRP3	(110)
Terpenoids	Pristimerin	Celastraceae and Hippocrateaceae	*In vivo, in vitro*	HFD Mice Mouse Bone-marrow cells	Disturbed the interaction between NEK7 and NLRP3	(111)
	Geniposide	Gardenia jasminoides Ellis	*In vivo, in vitro*	STZ mice Mouse podocytes	InhibitedAMPK/SIRT1/NF-κB, and NLRP3	(112)
	Genipin-1-β-d-gentiobioside	As above	*In vivo, in vitro*	STZ mice Mouse Podocytes	Inhibited AMPK/SIRT1/NF-κB, and NLRP3	(63)
	Swietenine	Swietenia macrophylla King	*In vivo, in vitro*	Db/db mice Human mesangial cells	InhibitedNF-κB/NLRP3/Caspase-1	(113)
	Artesunate	Artemisia annua	*In vitro*	HBZY-1	InhibitedTLR4/NF-κB/NLRP3	(114)
	Catalpol	Rehmannia glutinosa	*In vivo, in vitro*	STZ mice Mouse podocytes	InhibitedAMPK/SIRT1/NF-κB and NLRP3	(115)
	Andrographolide	Andrographis paniculata	*In vivo, in vitro*	STZ mice HK-2 cells	Inhibited NLRP3	(116)
	Triptolide	Tripterygium wilfordii Hook F	*In vitro*	Mouse podocytes	Inhibited NLRP3	(117)
Alkaloids	Berberine	Coptis and Phellodendron	*In vivo*	HFD/STZ hamsters	Regulated Nrf2/NLRP3 pathway	(28)

(Continued)

TABLE 2 Continued

	Compounds	Resource	*In Vivo/ in Vitro*	Model	Signaling Pathways	References
	Berberine	As above	*In vivo, in vitro*	STZ rats HK-2 cells	InhibitedNLRP3	(118)
	Piperine and Cepharanthine	Black pepper and Stephania cepharantha Hayata	*In vivo*	STZ Rats	Both decreased p38MAPK, p-JNK, TNF-α, TXNIP,NF-κB and NLRP3	(119)
	Solasonine	Solanummelongena	*In vitro*	MPC-5	Regulated Nrf2/NLRP3	(120)
	Rutaecarpine	Euodia rutaecarpine	*In vivo, in vitro*	Db/db mice MPC-5	Down-regulatedVEGFR2/NLRP3	(121)
Phenylpropanoids	Schisandrin A	Schisandra chinensis	*In vivo, in vitro*	STZ mice Human renal glomerular endothelial cells	Inhibited NLRP3 *via* AdipoR1/ AMPK-ROS/NLRP3	(122)
	Ferulic acid	Tomatoes, sweet corn, rice grain, Cimicifuga racemosa, Angelica sinensis, and ligustici chuanxiong rhizome	*In vivo*	STZ mice	Inhibited NLRP3	(123)
	Sauchinone	Saururus chinensis	*In vivo*	Human renal mesangial cells	Inhibited NF-κB, ROS, and NLRP3	(124)
Others	Crocin	Saffron	*In vivo*	STZ rats	InhibitedROS and NLRP3	(125)
	Pyrroloquinoline quinone	Fruits, vegetables, Gram-negative bacteria, and human breast milk	*In vivo, in vitro*	STZ mice HK-2 cells	ReducedROS and inhibited NF-κB/NLRP3	(126)
	Apocynin	Picrorhiza kurroa	*In vivo*	STZ Rats	InhibitedNLRP3/XIAP	(127)
	Diallyl trisulfide	garlic	*In vivo*	STZ rats	InhibitedROS/NLRP3/Caspase-1	(128)

HFD, high-fat diet; MPC-5, mouse podocyte cell-5; NEK7, never in mitosis A-related kinase 7; PAR-1, protease-activated receptor 1; STZ, streptozotocin; XIAP, X-linked inhibitor of apoptosis protein.

through the mtROS-TRX/TXNIP/NLRP3/IL-1β pathways. For DHQ, it has been shown to significantly reduce microalbuminuria, improve glucose and lipid metabolism dysfunction, and alleviate renal pathological changes in DKD rats. In renal cells induced by HG, DHQ significantly inhibits the activation of NLRP3 inflammasomes and renal fibrosis-associated proteins, reducing cell proliferation and oxidative stress (83).

Fisetin is a natural flavonol extracted from many fruits and vegetables, such as strawberries, apples, cucumbers, and onions (84). Studies indicate that fisetin possesses anti-inflammatory, anti-oxidant, anti-tumor, and cardiovascular protective effect (141–143). Dong et al. (84) demonstrated that fisetin ameliorated podocyte injury caused by HG, and mitigated renal injury in diabetic mice by suppressing NLRP3 inflammasome. Ge et al. (85) found that fisetin significantly attenuated the kidney damage in DKD mice, accompanied by a noticeable reduction in NLRP3 expression in the kidney. The protective effects of fisetin against DKD were also confirmed *in vitro* using palmitate-treated HK2 cells.

Liquiritigenin and Isoliquiritigenin (ISLQ) are flavonoid compounds extracted from Glycyrrhiza radix. Convincing evidence has shown that liquiritigenin and ISLQ possess a diversity of biological properties, such as anti-inflammatory, anti-oxidative, anti-hyperlipidemic, anti-tumor, and hepato-protective efficacity (144–148). Zhu et al. (86) found that liquiritigenin inhibited HG-induced extra-cellular matrix accumulation in glomerular mesangial cells. Moreover, liquiritigenin decreased HG-induced oxidative stress and inflammatory response *via* suppressing NF-κB/NLRP3 pathways. Alzahrani et al. (87) found that in DKD rats, ISLQ protected renal function and attenuated inflammation and collagen formation in kidney by restoring the Sirt-1/NF-κB balance, and downregulating NLRP3 expression.

Icariin (ICA) is obtained from Herba epimedii, and exerts quite a few pharmacological effects, such as anti-fibrosis and anti-inflammation (149). Ding et al. (26) confirmed that ICA increases Sesn2-induced mitophagy to inhibit NLRP3 inflammasome activation by the Keap1-Nrf2/HO-1 signaling pathway in DKD rats.

Calycosin is a representative isoflavone extracted from Radix Astragali (150). Many animal models have demonstrated that calycosin has reno-protective property (151). In diabetic SD rats, calycosin improves the deteriorated kidney functions and proteinuria. The possible mechanism is by regulating NF-κB/p65/NLRP3/TXNIP pathway (88).

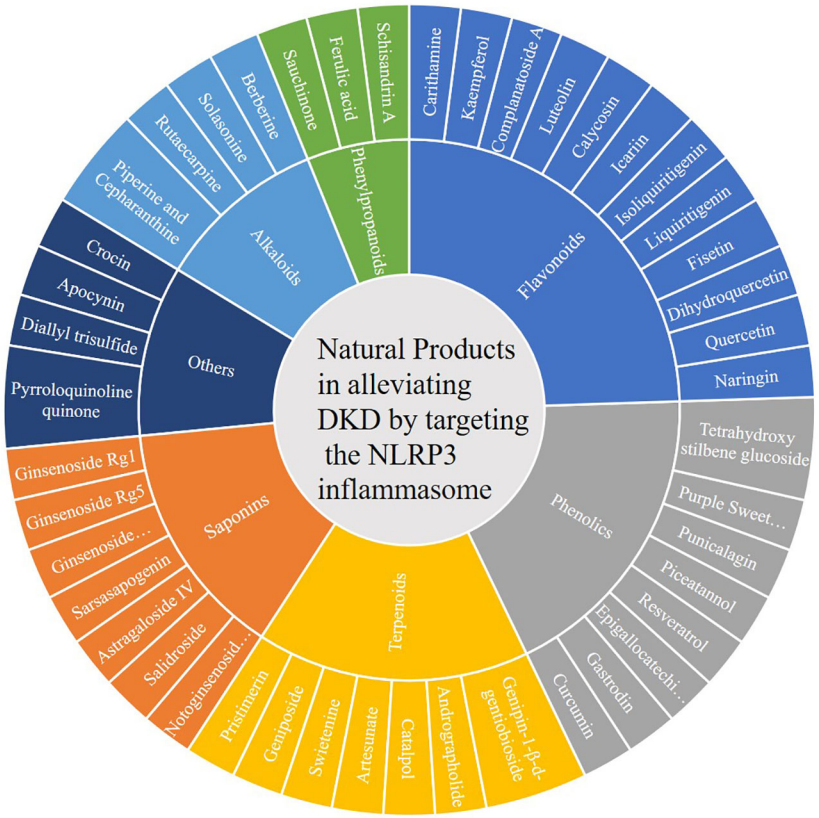

FIGURE 1
Natural products in alleviating DKD by targeting the NLRP3 inflammasome.

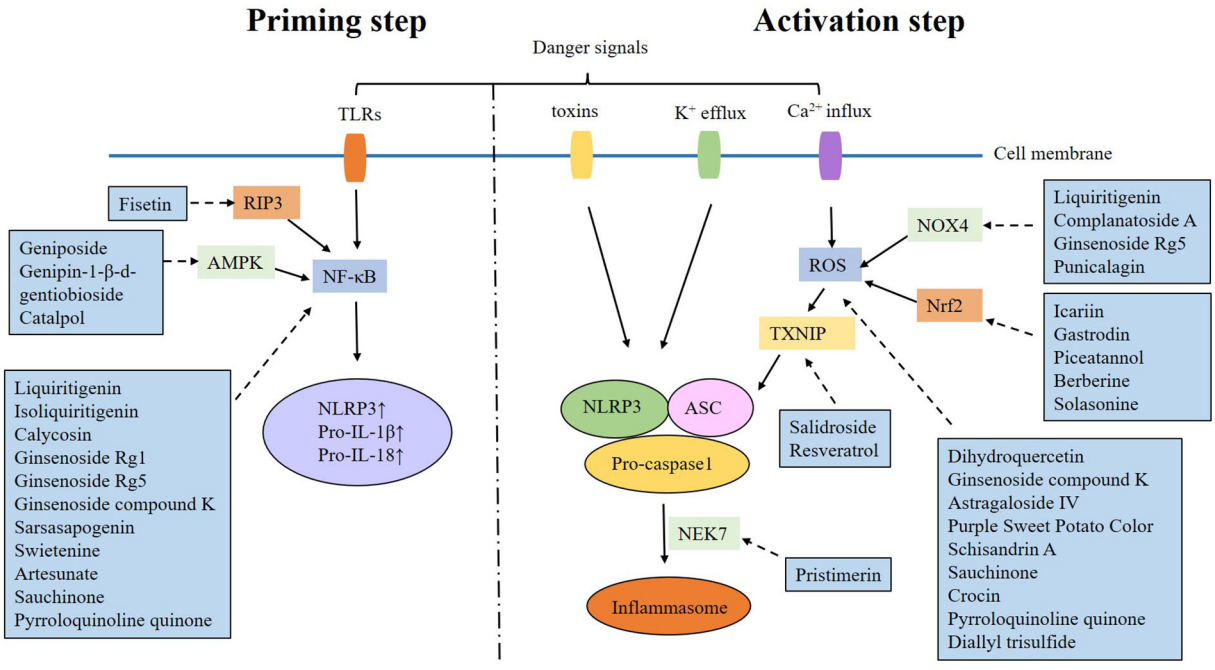

FIGURE 2
Mechanism of natural products alleviating DKD by targeting NLRP3 inflammasome.

Luteolin is a natural flavonoid present in several fruits and vegetables. It possesses many pharmacological properties, such as anti-inflammatory, antioxidant, anti-apoptotic, and anti-cancer effects (152–154). Yu et al. (89) revealed that luteolin could reduce cell apoptotic in HG-treated podocyte, and significantly inhibit the NLRP3 inflammasome activation and IL-1β production in HG-treated MPC-5 cells, suggesting that the anti-apoptotic effect was mostly related to NLRP3 inflammasome.

Complanatoside A (CA) is the ethanolic extract of Semen Astragali Complanati. It exhibits several biological activities, such as anti-oxidant and anti-apoptosis (155), and is widely used to fight against renal diseases in China. Ren et al. (90) found that CA mitigated the pathological lesions of glomeruli and tubular interstitium in DKD mice, it also reduced epithelial-mesenchymal transition (EMT) of HK-2 cells *via* blocking NOX4 expression and NLRP3 inflammasome activation.

Kaempferol is a natural compound with the formula $C_{15}H_{10}O_6$. It is mainly derived from the roots and stems of sand ginger, and is also distributed in plants such as tea, broccoli, and grapefruit. It is reported that kaempferol has antibacterial, anti-inflammatory, antioxidant, antitumor and many other pharmacological effects (156, 157). Studies revealed that kaempferol improved proteinuria and renal function in DKD rats. It also relieved renal tissue damage and cell apoptosis. Since the expression of NLRP3, ASC, and caspase-1 was decreased, it is probable that kaempferol can alleviate kidney damage in DKD rats by inhibiting the NLRP3 inflammasome (91).

Carithamine is a natural flavochrome extracted from the petals of safflower that has a variety of pharmacological properties, such as dilating coronary arteries, protecting myocardium and brain tissue, antioxidant, and immunoregulation (158). Gao et al. (92) found that intraperitoneal injection of carithamine alleviated proteinuria in DKD rats by downregulating the expression of NLRP3 and Caspase-1.

4.2 Saponins

Saponins are a class of glycosides whose aglycones are triterpenoids or spirostanes. They are mainly found in terrestrial higher plants but can also be found in marine organisms such as starfish and sea cucumbers (159). Saponins are generally considered beneficial for the cardiovascular system and diabetes (160).

Ginsenoside is the major active constituent of ginseng, which belongs to perennial herbaceous plant and is used as a traditional herb medicine for many years (161). Ginsenoside owns many biological activities, including anti-inflammation, anti-tumor, and anti-diabetes (162–164). Ginsenoside Rg1 and Ginsenoside Rg5 are the representative monomers of ginsenoside (165, 166). Wang et al. (93) found that ginsenoside Rg1 inhibited pyroptosis in hyperlipid-induced podocytes, and this effect was also observed in the kidneys of rats with DKD. The possible mechanism was by down-regulating the mTOR/NF-κB/NLRP3 pathway. Zhu et al. (94) demonstrated that ginsenoside Rg5 reduced oxidative stress and the activation of NLRP3 inflammasome, thereby mitigated kidney damage in DKD mice. Ginsenoside compound K(CK) is the final metabolite of diol-type ginsenosides such as Rb1 and Rb2 by the action of intestinal flora (167). Song et al. (95) proved that CK significantly improved renal function and urinary protein excretion of DKD mice, and the proliferation of glomerular mesangial matrix was also decreased. Moreover, the protective effect of CK is possibly due to suppression of NF-κB/p38 and ROS/NLRP3 signaling pathway.

Sarsasapogenin (Sar) is a steroidal sapogenin isolated from Anemarrhena asphodeloides Bunge. It is believed to have antiplatelet, antithrombotic, and anti-inflammatory propertis (168–171). Tang et al. (96) found that Sar significantly improved kidney function in DKD rats, and renal histopathology showed that it reduced mesangial cell proliferation, inhibited the activation of NLRP3 inflammasome and NF-κB. Liu et al. (97) also found that Sar can markedly ameliorate DKD in rats *via* ameliorating the NLRP3 inflammasome activation and AGEs–receptor for AGE (RAGE) interaction.

Astragaloside IV (AS–IV) is the primary active ingredient in Astragalus membranaceus, a traditional herb medicine. It has been identified to have anti-inflammatory and anti-oxidant effects and is widely used to deal with diabetes and cardiovascular diseases (172, 173). Feng et al. (98) demonstrated that AS-IV blocked NLRP3 inflammasome activation, and improved renal function and podocytes damage in db/db mice, exerting a reno-protective effect. Zhao et al. (99) observed that AS–IV reduced NLRP3 expression in HG exposed mouse glomerular mesangial cells.

Salidroside (SAL) is the predominant component of Rhodiola rosea, an herbal plant with a wide range of pharmacological effects, including anti-altitude sickness, anti-oxidant, and anti-diabetes (174–176). SAL also exerts beneficial effects on DKD (177). Wang et al. (100) showed that SAL inhibited TXNIP/NLRP3 signaling pathway in rat glomerular mesangial cells.

Notoginsenoside Fc (Fc) is a novel saponin extracted from Panax notoginseng with excellent anti-platelet aggregation ability (178). It is reported that Fc reduced albuminuria, alleviated renal failure, and relieved podocyte injury in db/db mice by inhibiting the NLRP3 inflammasomes (101).

4.3 Phenolics

Phenolics are a class of chemicals that contain aromatic rings and hydroxyl groups. They are widely distributed in nature, especially in fruits, vegetables, cereals, flowers, spices, and teas (179). In the past decades, the potential value of phenolics in healing DKD has been explored.

Tetrahydroxy stilbene glucoside (TSG) is derived from Polygoni Multiflori Radix. TSG has been shown to reduce blood cholesterol, protect the liver, possess antioxidant abilities, and exhibit anti-atherosclerotic properties (180). Li et al. (102) demonstrated that TSG prevented podocytes apoptosis in HG condition, and it was partly through the blockade of NLRP3 inflammasome.

Gastrodin is a natural compound isolated from the dried root of Gastrodia elata (181). It has been found to exert anti-inflammatory, antioxidative, and neuroprotective effects (182). Huang et al. (103) proved that gastrodin halted the activation of NLRP3 inflammasome in HG-treated podocytes, which reduced renal inflammation and oxidative stress.

Epigallocatechin-3-gallate (EGCG) is a polyphenolic component found in tea leaves with strong anti-inflammatory property. Yang et al. (104) confirmed that EGCG can ameliorate renal dysfunction and renal histopathological injury in DKD rats. Furthermore, the reno-protective effects of EGCG are mainly related to the suppression of endoplasmic reticulum stress-mediated NLRP3 inflammasome overactivation.

Resveratrol is a polyphenolic compound mainly derived from plants such as grapes, peanuts, mulberries, and Polygonum cuspidatum (183). It is reported to be a strong scavenger of ROS (184), and has the ability to ameliorate hyperglycemia mediated renal dysfunction (185). Xiao et al. (105) revealed that in diabetic models with acute kidney injury, the primary mechanism is attributed to TXNIP/NLRP3 activation stimulated by oxidative stress.

Piceatannol is a polyphenol compound sharing a similar chemical structure to resveratrol. It is mainly found in grapes, sugar cane, white tea, rhubarb, passion fruit and blueberries (186). Piceatannol is considered to have anticancer, anti-atherogenic, anti-oxidative, anti-inflammatory, anti-microbial and estrogenic activities, and is widely used in the treatment of heart disease, leukemia and cancer (187–190). Yao et al. found that piceatannol can inhibit apoptosis, inflammation and oxidative stress of podocytes under HG condition. The possible mechanism is that it inhibits the activation of NLRP3 inflammation by promoting Nrf2 nuclear translocation and up-regulating Nrf2 expression (106).

Curcumin, a chief component of Curcuma longa, has been consumed by humans as a spice. It exhibits powerful anti-inflammatory and anti-cancer properties (191). The reno-protective effect of curcumin in DKD rats has been verified (192, 193). Lu et al. (107) found that curcumin inhibited the activation of NLRP3 inflammasome in db/db mice, similar to that in HG-induced HK-2 cells, resulting in alleviation of DKD.

Punicalagin (PU) is the main component of pomegranate polyphenols and is found abundantly in pomegranate, myrobalan, leaves of yellow wood, and tropical almond (194, 195). PU exhibits strong antioxidative, anti-inflammatory, and antineoplastic properties (196, 197). An et al. (108) proved that PU reduced kidney damage in high-fat diet (HFD)/streptozotocin (STZ) mice, possibly by downregulating the NOX4/TXNIP/NLRP3 pathway.

Purple Sweet Potato Color (PSPC) is a natural flavonoid leached from the rhizome of purple sweet potatoes. It has strong anti-oxidant and anti-inflammatory abilities that can protect the brain, liver, and kidney (198–200). Zheng et al. (109) found that PSPC exert renal protection in HFD-treated mice by inhibiting ROS-Triggered NRLP3 inflammation.

Grape seed proanthocyanidin is a polyphenol compound extracted from grape seeds, which is one of the most efficient antioxidants found to date. It has anti-radiation, anti-cancer, anti-atherosclerosis and anti-diabetic effects (201–203). Qiu et al. (110) found that in DKD rats with ischemia-reperfusion injury, intraperitoneal injection of grape seed proanthocyanidin could improve renal function and alleviate renal oxidative stress, possibly by inhibiting NLRP3 gene expression.

4.4 Terpenoids

Terpenoids are olefin compounds with an isoprene unit (C_5 unit) as the basic structural unit. They exist widely in nature and are the main components of some plant fragrances, resins and pigments. Terpenoids have diverse physicochemical properties and biological activities, and exhibit promising efficacy in the management of DKD (204).

Pristimerin (Pri) is a quinonoid triterpene isolated from Celastraceae and Hippocrateaceae (205). It shows excellent anti-bacterial, anti-fungal, anti-inflammatory, and anti-tumor abilities (206, 207), and has been widely used in treating colitis, sepsis, and neuroinflammation (208, 209). Zhao et al. (111) found that intraperitoneal injection of Pri in an HFD-induced diabetic mouse model reversed metabolic disorders by restraining the activation of the NLRP3 inflammasome. They further illustrated that this was associated with disturbing the interaction between never in mitosis A-related kinase 7 (NEK7) and NLRP3 *in vitro*.

Geniposide (GE) and genipin-1-β-d-gentiobioside (GG) are active ingredients extracted from the fruit of Gardenia jasminoides Ellis. Many researches on GE have proved that it can lower blood glucose and lose weight, it also has anti-inflammatory, anti-tumor, neuroprotective, and myocardial protective effects (210–212). Hu et al. (213) revealed that GE can alleviated the development of STZ-induced DKD. Li et al. (112) confirmed that GE down-regulated the expression of NLRP3, ASC, IL-1, and Caspase-1β in DKD mice, possibly through down-regulation of the AMPK/SIRT1/NF-κB signaling pathway. GG has a chemical structure similar to that of GE, except for one more glycosidic group. Li et al. (63) suggested that GG promoted podocyte survival and attenuated renal damage in DKD mice, with the reno-protective effect related to the AMPK/SIRT1/NF-κB/NLRP3 pathway.

Swietenine (Swi) is derived from the Swietenia macrophylla King plant and possesses outstanding anti-bacterial, anti-inflammatory, anti-oxidant, anti-tumor, and anti-diabetic properties (214–216). Duan et al. (113) found that Swi remarkably improved renal function and suppressed inflammatory response in DKD mice. The signal pathway that may be involved is NF-κB/NLRP3/Caspase-1 axis.

Artesunate (ART) is a major derivative of artemisinin isolated from Artemisia annua (217). Studies have revealed that ART possesses a wide range of biological activities, including anti-malarial, anti-oxidative, anti-inflammatory, and anti-tumor effects (218–220). Sun et al. (114) demonstrated that ART inhibited TLR4/NF-κB/NLRP3 pathway, thereby ameliorating glomerular mesangial cell injury under HG conditions.

Catalpol (Cat) is an iridoid glycoside rich in the roots of Rehmannia glutinosa, exhibiting potent anti-oxidant, anti-tumor, anti-inflammatory, and anti-diabetic effects (221, 222). There are accumulating evidence suggesting that Cat can be used to treat DKD (223). Chen et al. (115) revealed that Cat effectively attenuated kidney damage in DKD mice, it can reduce oxide stress and inflammation by targeting AMPK/SIRT1/NF-κB pathway.

Andrographolide is a labdane diterpenoid isolated from Andrographis paniculata Nees with numerous biological activities, including anti-inflammatory, anti-tumor, and anti-diabetic capacities (224). Li et al. (225) found that andrographolide attenuated DKD progression by inhibiting oxidative stress and inflammation in mesangial cells. Moreover, they found that andrographolide significantly reduced HG-induced apoptosis, EMT, and fibrosis *via* blocking NLRP3 inflammasome activation (116).

Triptolide (TP) is the main active ingredient isolated from Tripterygium wilfordii Hook F. It exhibits excellent anti-inflammatory and anti-apoptosis abilities, as well as anti-cancer and anti-diabetic activities (226–228). Wu et al. (117) discovered that TP can block the activation of NLRP3 inflammasome and alleviate EMT in podocytes under HG condition, which may be one of the mechanisms by which TP alleviates podocytes injury in DKD.

4.5 Alkaloids

Alkaloids are a class of nitrogen-containing basic organic compounds, which mainly exist in plant. Alkaloids have abundant medicinal value, possessing anti-arrhythmia, anti-hypertensive, analgesic, anti-inflammatory, and anti-cancer properties (229, 230).

Berberine (BBR), also known as berberine hydrochloride or berberine sulphate, is an alkaloid derived from Coptis. It shows anti-inflammatory, anti-oxidant, anti-diabetic, and hypolipidemic activities (231). It is reported that BBR relieves DKD by inhibiting mesangial cell proliferation and ameliorating tubulointerstitial fibrosis (232, 233). Ding et al. (28) revealed that BBR can reduce oxidative stress and antagonize inflammation by regulating Nrf2/NLRP3 pathway. Ma et al. (118) also confirmed that BBR could inhibit HG induced EMT and renal interstitial fibrosis by down-regulating the NLRP3 inflammasome in HK-2 cells.

Piperine (Pip) is a bioactive alkaloid mainly present in black pepper. It has many pharmaceutical effects including promoting digestion, lowering lipid peroxidation, as well as anti-inflammatory, anti-cancer, and antioxidant (234–236). Cepharanthine (CEP) is a natural alkaloid extracted from Stephania cepharantha Hayata, and possesses anti-oxidative, anti-inflammatory, anti-proliferative, anti-metastatic and anti-atherosclerosis properties (237, 238). Samra et al. (119) found that CEP, Pip or their combination noticeably improves renal function and proteinuria in diabetic rats, accompanied by down-regulation of NF-κB and NLRP3.

Solasonine (SS) is a natural glycoalkaloid isolated from Solanummelongena. It has been proved to possess anti-inflammatory, anti-cancer, and neuroprotective properties (239–241). Zhang et al. (120) revealed that SS alleviated cell apoptosis, reduced pyroptosis and oxidative injury in podocytes induced by HG. The possible mechanism may be through regulating the Nrf2/NLRP3 signaling pathway.

Rutaecarpine is an important active component of Euodia rutaecarpine (242). Numerous studies have shown that rutaecarpine has anti-inflammatory, anti-atherosclerosis, and anti-cancer pharmacological effects (243–245). Hu et al. (121) found that rutaecarpine effectively alleviated renal damage in db/db mice, along with the reduced expression of NLRP3/ASC/IL-18/IL-1β in the kidney. *In vitro* studies also confirmed that rutaecarpine can inhibit NLRP3/ASC/IL-18/IL-1β in MPC-5 and reduce programmed cell necrosis, which suggested that rutaecarpine may be protective to DKD through NLRP3-dependent pathway.

4.6 Phenylpropanoids

Phenylpropanoids are one of the main phenolic acids widely distribution in plants, with the C6-C3 carbon skeleton as core structure (246). They are mainly found in fruits, vegetables, cereal grains, beverages, spices and herbs. Phenylpropanoids are known to have multifaceted effects, including antimicrobial, antioxidant, anti-inflammatory, anti-diabetic, anticancer activities (247, 248). Their therapeutic effects on DKD are also being explored.

Schisandra chinensis is the dried ripe fruits of Schisandra chinensis (Turcz.) Baill. It is both a health food and a traditional herb medicine (249, 250).. Schisandrin A is the main lignan derived from Schisandra chinensis, which exerts anti-oxidative, anti-apoptosis, and sedative abilities (251, 252). Wang et al. (122) revealed that schisandrin A decreased ROS overproduction and inhibited inflammation in DKD mice. It also reduced HG-induced ferroptosis and ROS-mediated pyroptosis by mitochondrial damage in human renal glomerular endothelial cells. The expression of TXNIP and NLRP3 was down-regulated by Schisandrin A, suggesting that Schisandrin A attenuated DKD by suppressing TXNIP/NLRP3 signaling pathway.

Ferulic acid (FA) is a natural derivative of caffeic acid commonly found in vegetables, especially in tomatoes, corns, and rices. It is also the main active ingredient of many traditional herbal medicines, involving Cimicifuga racemosa, Angelica sinensis, and ligustici chuanxiong rhizome (253). FA exhibits a wide range of therapeutic effects, including scavenging free radicals, antioxidant properties, and anti-cancer, anti-inflammatory, anti-fibrotic, and reno-protective effects against cardiovascular diseases, neurodegenerative diseases, and diabetes (253–256). It is also revealed that FA has reno-protective effects in DKD rats by antioxidation, anti-inflammation and anti-fibrosis (257–259). Ma et al. (123) further proved that FA reduced the expressions of p62, NLRP3 and IL-1β in renal tissues of DKD mice and suppressed inflammation.

Sauchinone is a biologically active lignin extracted from Saururus chinensis. Studies have shown that it has powerful anti-oxidant, anti-inflammatory, anti-apoptosis, anti-cancer and anti-obesity abilities (260–263). Yoon et al. (124) found that sauchinone improved angiotensin II-induced mesangial inflammation by inhibiting the NLRP3 inflammasome.

4.7 Others

Crocin is a carotenoid compound mainly exist in saffron, which belongs to the iris family, a perennial stemless herb. Previous studies have shown that crocin has a variety of pharmacological effects, including the inhibition of cancer growth, inflammatory responses,

apoptosis, and oxidative stress (264–268). Crocin also has reno-protective effects (269). Zhang et al. (125) demonstrated that Crocin improved diabetic kidney dysfunction and renal fibrosis in STZ rat. Additionally, Crocin reduced excessive ROS production and decreased the synthesis of pro-inflammatory factors by inhibiting the activation of the NLRP3 inflammasome.

Pyrroloquinoline quinone (PQQ) is the third coenzyme of oxidoreductase discovered so far, which exists widely in plants, bacteria, animals, and human (270). The confirmed biological abilities of PQQ include antioxidant, neuro-protection, and immunoregulation (271–273). Qu et al. (126) demonstrated that PQQ down-regulated the expression of NLRP3, caspase-1, IL-1β, and attenuated renal fibrosis by alleviating mitochondrial dysfunction, reducing ROS production in STZ mice and HG induced HK-2 cells.

Apocynin is a compound isolated from the root of the medicinal herb Picrorhiza kurroa (274, 275). It is used as an antioxidant due to the ability to inhibit NADPH oxidase activity and reduce ROS production (276, 277). Xin et al. (127) found that in rats with DKD, apocynin improved renal function and attenuated renal fibrosis. This effect was likely due to the down-regulation of the NLRP3/X-linked inhibitor of apoptosis protein (XIAP) signaling pathway.

Diallyl trisulfide (DATS), one of the main allyl sulfur compounds exist in garlic, possesses considerable anti-oxidant, anti-inflammatory, anti-fibrosis, and anti-fungal activities (278–280). Shen et al. (128) confirmed that DATS alleviated renal damage in DKD rats, and the expressions of ROS, NLRP3, ASC, Caspase-1, IL-1β and IL-18 were decreased, which suggested that DATS may be effective in treating DKD by inhibiting ROS/NLRP3/Caspase-1 pathway.

5 Conclusion

Inflammation plays a crucial role in the pathogenesis of DKD, and the NLRP3 inflammasome is regarded as a key regulator of inflammation in DKD. Various signaling pathways are involved in the activation of NLRP3 inflammasome, including NF-κB, ROS/TXNIP, ncRNAs. However, specific mechanisms and crosstalk between them require further investigation. Many natural products exhibit excellent anti-inflammatory properties, and may alleviate DKD by inhibiting the activation of NLRP3 inflammasome. However, most studies are mainly limited to *in vitro* and animal experiments. With improved understanding of the regulatory network of NLRP3 inflammasome, and better understanding of the pharmacological mechanism of natural products, more clinical trials on the use of natural products in the treatment of DKD are expected in the future.

Author contributions

All authors contributed significantly to this work and approved the publication of the manuscript. PL devised the research plan. YW, ZS, and MW wrote the manuscript. PL and YW modified and polished the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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